

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: UCKUN ET AL. Examiner: UNKNOWN  
Serial No.: 10/726,073 Group Art Unit: UNKNOWN  
Filed: DECEMBER 1, 2003 Docket: 12152.15USC6  
Due Date: MARCH 1, 2003  
Title: ARYL PHOSPHATE DERIVATIVES OF D4T HAVING ANTI-HIV ACTIVITY



CERTIFICATE UNDER 37 CFR 1.8:

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail, with sufficient postage, in an envelope addressed to: , Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on March 1, 2004.

By: 

Name: KATE GANNON

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**23552**

PATENT TRADEMARK OFFICE

Sir:

We are transmitting herewith the attached:

- ☒ Transmittal Sheet in duplicate containing Certificate of Mailing
- ☒ Information Disclosure Statement, Form 1449
- ☒ Return postcard

Please consider this a PETITION FOR EXTENSION OF TIME for a sufficient number of months to enter these papers or any future reply, if appropriate. Please charge any additional fees or credit overpayment to Deposit Account No. 13-2725. A duplicate of this sheet is enclosed.

MERCHANT & GOULD P.C.  
P.O. Box 2903, Minneapolis, MN 55402-0903  
612.332.5300

By: 

Name: Anna M. Nelson

Reg. No.: 48,935

ANelson:PLSklg



S/N 10/726,073

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

|             |  |                 |              |
|-------------|--|-----------------|--------------|
| Applicant:  | UCKUN ET AL.   | Examiner:       | UNKNOWN      |
| Serial No.: | 10/726,073   | Group Art Unit: | UNKNOWN      |
| Filed:      | DECEMBER 1, 2003   | Docket No.:     | 12152.15USC6 |
| Title:      | ARYL PHOSPHATE DERIVATIVES OF D4T HAVING ANTI-HIV ACTIVITY |                 |              |

CERTIFICATE UNDER 37 CFR 1.8:

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail, with sufficient postage, in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on March 1, 2004.

By: 

Name: KATE CANNON

INFORMATION DISCLOSURE STATEMENT (37 C.F.R. § 1.97(b))

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

With regard to the above-identified application, the items of information listed on the enclosed Form 1449 are brought to the attention of the Examiner.

This statement should be considered because it is submitted within three months of the filing date of the above-identified application, which is not an application under 37 C.F.R. § 1.53(d). Accordingly, no fee is due for consideration of the items listed on the enclosed Form 1449.

In accordance with 37 C.F.R. § 1.98(a)(2) and § 1.98(d), copies have been provided only for those items listed on the enclosed Form 1449 that have not previously been cited by or submitted to the U.S. Patent and Trademark Office in parent application, U.S. Serial No. 09/548,492 filed on April 13, 2000, now U.S. Patent No. 6,528,495 B1, issued on March 4, 2003.

No representation is made that a reference is "prior art" within the meaning of 35 U.S.C. §§ 102 and 103 and Applicants reserve the right, pursuant to 37 C.F.R. § 1.131 or otherwise, to establish that the reference(s) are not "prior art." Moreover, Applicants do not represent that a reference has been thoroughly reviewed or that any relevance of any portion of a reference is intended.

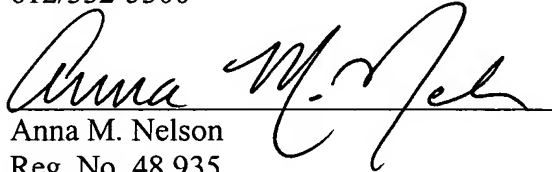
Consideration of the items listed is respectfully requested. Pursuant to the provisions of M.P.E.P. 609, it is requested that the Examiner return a copy of the attached Form 1449, marked as being considered and initialed by the Examiner, to the undersigned with the next official communication.

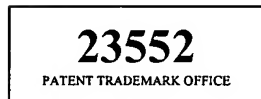
Please charge any additional fees or credit any overpayment to Deposit Account No. 13-2725.

Respectfully submitted,

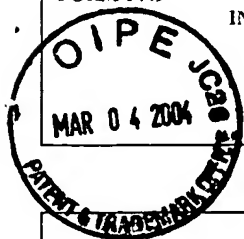
MERCHANT & GOULD P.C.  
P.O. Box 2903  
Minneapolis, MN 55402-0903  
612/332-5300

Date: March 1, 2004

  
Anna M. Nelson  
Reg. No. 48,935  
AMN:PLSklg



|  |                                |                                   |
|--|--------------------------------|-----------------------------------|
| FORM 1449*<br><b>INFORMATION DISCLOSURE STATEMENT</b><br><br><b>IN AN APPLICATION</b><br>(Use several sheets if necessary) | Docket Number:<br>12152.15USC6 | Application Number:<br>10/726,073 |
|  | Applicant: UCKUN ET AL.        |                                   |
|  | Filing Date: 12/01/2003        | Group Art Unit: UNKNOWN           |



| U.S. PATENT DOCUMENTS |              |            |                  |       |          |                            |
|-----------------------|--------------|------------|------------------|-------|----------|----------------------------|
| EXAMINER INITIAL      | DOCUMENT NO. | DATE       | NAME             | CLASS | SUBCLASS | FILING DATE IF APPROPRIATE |
|                       | 4,707,362    | 11/17/1987 | Nuwayser         |       |          |                            |
|                       | 4,841,039    | 06/20/1989 | Chu et al.       |       |          |                            |
|                       | 5,069,906    | 12/03/1991 | Cohen et al.     |       |          |                            |
|                       | 5,595,980    | 01/21/1997 | Brode et al.     |       |          |                            |
|                       | 5,659,023    | 08/19/1997 | Alexander et al. |       |          |                            |
|                       | 5,672,698    | 09/30/1997 | Chen et al.      |       |          |                            |
|                       | 5,750,729    | 05/12/1998 | Alexander et al. |       |          |                            |
|                       | 6,030,957    | 02/29/2000 | Uckun et al.     |       |          |                            |
|                       | 6,350,736 B1 | 02/26/2002 | Uckun et al.     |       |          |                            |
|                       | 6,537,975 B1 | 03/25/2003 | Uckun et al.     |       |          |                            |
|                       | 6,503,890 B1 | 01/07/2003 | Uckun            |       |          |                            |
|                       | 6,528,495 B1 | 03/04/2003 | Uckun et al.     |       |          |                            |
|                       | 6,670,336 B1 | 12/30/2003 | Uckun et al.     |       |          |                            |

| FOREIGN PATENT DOCUMENTS |              |            |                    |       |          |             |    |
|--------------------------|--------------|------------|--------------------|-------|----------|-------------|----|
|                          | DOCUMENT NO. | DATE       | COUNTRY            | CLASS | SUBCLASS | TRANSLATION |    |
|                          |              |            |                    |       |          | YES         | NO |
|                          | 6189998      | 07/12/1994 | JP (Abstract only) |       |          | X           |    |
|                          | WO 94/14831  | 07/07/1994 | PCT                |       |          |             |    |
|                          | WO 96/29336  | 09/26/1996 | PCT                |       |          |             |    |
|                          | WO 97/42962  | 11/20/1997 | PCT                |       |          |             |    |

| OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.) |  |  |
|--|--|--|
|  |  | Alexander, P. et al., "Synthesis and Antiviral Activity of Pyranosylphosphonic Acid Nucleotide Analogues", <i>J. Med. Chem.</i> , 39:1321-1330 (March 15, 1996)  |
|  |  | Balzarini, J. et al, "Differential Patterns of Intracellular Metabolism of 2', 3'-Didehydro-2', 3'-dideoxythymidine and 3'-Azido-2', 3'-dideoxythymidine, Two Potent Anti-human Immunodeficiency Virus Compounds", <i>J. Biol.Chem.</i> , 264(11):6127-6133 (April 15, 1989) |
|  |  | Bourinbaier, A. et al., "Anti-HIV Effect of Gramicidin in Vitro: Potential for Spermicide Use", <i>Life Sciences</i> , 54(1):PL5-9 (1994)  |
|  |  | Bourinbaier, A. et al., "Comparative in vitro Study of Contraceptive Agents with Anti-HIV Activity: Gramicidin, nonoxynol-9, and gossypol", <i>Contraception</i> , 49(2):131-137 (February 1994)   |
|  |  | Burkman, L., "Discrimination Between Nonhyperactivated and Classical Hyperactivated Motility Patterns in Human Spermatozoa Using Computerized Analysis", <i>Fertility and Sterility</i> , 55(2):363-371 (February 1991)  |

|   |                 |
|---|-----------------|
| EXAMINER  | DATE CONSIDERED |
| EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form for next communication to the Applicant. |                 |

|   |                         |                         |
|---|-------------------------|-------------------------|
| <b>FORM 1449*</b><br><br><b>INFORMATION DISCLOSURE STATEMENT</b><br><br><b>IN AN APPLICATION</b><br><br>(Use several sheets if necessary) | Docket Number:          | Application Number:     |
|   | 12152.15USC6            | 10/726,073              |
|   | Applicant: UCKUN ET AL. |                         |
|   | Filing Date: 12/01/2003 | Group Art Unit: UNKNOWN |

|  |   |
|--|---|
|  | D'Cruz, O.J. et al., "Aryl Phosphate Derivatives of Bromo-Methoxy-Azidothymidine Are Dual-Function Spermicides with Potent Anti-Human Immunodeficiency Virus", <i>Biology of Reproduction</i> , Vol. 59, pp. 503-515 (1998)   |
|  | D'Cruz, O. et al., " $\beta_2$ -Integrin (CD11b/CD18) Is the Primary Adhesive Glycoprotein Complex Involved in Neutrophil-Mediated Immune Injury to Human Sperm", <i>Biology of Reproduction</i> , 53(5):1118-1130 (November 1995).   |
|  | D'Cruz, O. et al., "Spermicidal Activity of Metallocene Complexes Containing Vanadium (IV) in Humans", <i>Biology of Reproduction</i> , 58(6):1515-1526 (June 1998)   |
|  | Dicker, D. et al., "The Value of Repeat Hysteroscopic Evaluation in Patients with Failed In Vitro Fertilization Transfer Cycles", <i>Fertility and Sterility</i> , 58(4):833-835 (October 1992)   |
|  | Erice, A. et al., "Anti-Human Immunodeficiency Virus Type 1 Activity of an Anti-CD4 Immunoconjugate Containing Pokeweed Antiviral Protein", <i>Antimicrobial Agents and Chemotherapy</i> , 37(4):835-838 (April 1993).  |
|  | Erlandsen, S. et al., "Membrane Fixation for High-Resolution Low-Voltage SEM: Studies on <i>Giardia</i> , Rat Spermatozoa, and Mouse Macrophages", <i>Scanning</i> , 11(4) 169-175 (July/August 1989)   |
|  | Furman, P. et al., "Phosphorylation of 3'-azido-3'-deoxythymidine and selective interaction of the 5'-triphosphate with Human Immunodeficiency Virus Reverse Transcriptase", <i>Proc. Natl. Acad. Sci. USA</i> , Vol. 83, pgs. 8333-8337 (November 1986)                                      |
|  | Hao, Z. et al., "Factors Determining the Activity of 2', 3'-Dideoxynucleosides in Suppressing Human Immunodeficiency Virus In Vitro", <i>Molecular Pharmacology</i> , 34(4):431-435 (October 1988)  |
|  | Jan, S. et al., "AZT-5'-(p-bromophenyl methoxyalaninyl phosphate) as a potent and non-toxic anti-human immunodeficiency virus agent", <i>Antiviral Chemistry &amp; Chemotherapy</i> , Vol. 10, pp. 47-52 (©1999 International Medical Press).   |
|  | Jan, S.T., et al., "Synthesis of dual function (5R,6R)- and (5S,6S)- 5-bromo-6-methoxy-5, 6-dihydro-AZT-5'-(para-bromophenyl methoxyalaninyl phosphate) as novel spermicidal and anti-HIV agents", <i>Antiviral Chemistry &amp; Chemotherapy</i> , Vol. 10, pp. 39-46 (July 9, 1999)          |
|  | Kumar, R. et al., "Synthesis, In Vitro Biological Stability, and Anti-HIV Activity of 5-Halo-6-alkoxy (or azido)-5, 6-dihydro-3'-azido-3'-deoxythymidine Diastereomers as Potential Prodrugs to 3'-Azido-3'-deoxythymidine (AZT)", <i>J. Med. Chem.</i> , 37(25):4297-4306 (December 9, 1994) |
|  | Mansuri, M. et al., "1-(2, 3-Dideoxy- $\beta$ -D-glycero-pent-2-enofuranosyl) Thymine. A highly Potent and Selective Anti-HIV Agent", <i>J. Med. Chem.</i> , 32(2):461-466 (February 1989)  |
|  | McGuigan, C. et al., "Aryl Phosphate Derivatives of AZT Inhibit HIV Replication in Cells Where the Nucleoside is Poorly Active", <i>Bioorganic &amp; Medicinal Chemistry Letters</i> , 2(7):701-704 (1992)  |
|  | McGuigan, C. et al., "Aryl Phosphate Derivatives of AZT Retain Activity Against HIV1 in Cell Lines Which are Resistant to the Action of AZT", <i>Antiviral Research</i> , 17(4):311-321 (April 1, 1992)   |
|  | McGuigan, C. et al., "Aryl Phosphoramidate Derivatives of d4T Have Improved Anti-HIV Efficacy in Tissue Culture and May Act by the Generation of a Novel Intracellular Metabolite", <i>J. Med. Chem.</i> , 39(8):1748-1753 (April 12, 1996)   |
|  | McGuigan, C. et al., "Intracellular Delivery of Bioactive AZT Nucleotides by Aryl Phosphate Derivatives of AZT", <i>J. Med. Chem.</i> , 36(8):1048-1052 (April 16, 1993)  |
|  | McGuigan, C. et al., "Phosphoramidates as Potent Prodrugs of Anti-HIV Nucleotides: Studies in the Amino Region", <i>Antiviral Chemistry &amp; Chemotherapy</i> , 7(1):31-36 (1996)  |
|  | McGuigan, C. et al., "Phosphoramidate Derivatives of AZT as Inhibitors of HIV: Studies on the Carboxyl Terminus", <i>Antiviral Chemistry &amp; Chemotherapy</i> , 4(2):97-101 (1993)  |
|  | McGuigan, C. et al., "Phosphoramidate Derivatives of d4T with Improved Anti-HIV Efficacy Retain Full Activity in Thymidine Kinase-Deficient Cells", <i>Bioorganic &amp; Medicinal Chemistry Letters</i> , 6(10):1183-1186 (May 21, 1996)  |

|   |                 |
|---|-----------------|
| EXAMINER  | DATE CONSIDERED |
| EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form for next communication to the Applicant. |                 |

|   |                                |                                   |
|---|--------------------------------|-----------------------------------|
| <b>FORM 1449*</b><br><br><b>INFORMATION DISCLOSURE STATEMENT</b><br><br><b>IN AN APPLICATION</b><br><br>(Use several sheets if necessary) | Docket Number:<br>12152.15USC6 | Application Number:<br>10/726,073 |
|   | Applicant: UCKUN ET AL.        |                                   |
|   | Filing Date: 12/01/2003        | Group Art Unit: UNKNOWN           |

|  |  |
|--|--|
|  | McIntee, E. et al., "Probing the Mechanism of Action and Decomposition of Amino Acid Phosphomonoester Amides of Antiviral Nucleoside Prodrugs", <i>J. Med. Chem.</i> , 40(21):3323-3331 (October 10, 1997)   |
|  | Niruthisard, S. et al., "The Effects of Frequent Nonoxynol-9 Use on the Vaginal and Cervical Mucosa", <i>Sexually Transmitted Diseases</i> , 18(3):176-179 (July-September 1991)   |
|  | Siddiqui, A. et al., "Design and Synthesis of Lipophilic Phosphoramidate d4T-MP Prodrugs Expressing High Potency Against HIV in Cell Structure: Structural Determinants for in Vitro Activity and QSAR", <i>J. Med. Chem.</i> , 42:4122-4128 (1999)  |
|  | Siddiqui, A. et al., "The Presence of Substituents on the Aryl Moiety of the Aryl Phosphoramidate Derivative of d4T Enhances Anti-HIV Efficacy in Cell Culture: A Structure-Activity Relationship", <i>J. Med. Chem.</i> , 42:393-399 (1999)   |
|  | Stoffel, M. et al., "Improved Preservation of Rat Epididymal Sperm for High-Resolution Low-Voltage Scanning Electron Microscopy (HR-LVSEM)", <i>Molecular Reproduction and Development</i> , 34(2):172-182 (February 1993)   |
|  | Tryphonas, L. et al., "Morphologic Evidence for Vaginal Toxicity of Delfen Contraceptive Cream in the Rat", <i>Toxicology Letters</i> , 20(3):289-295 (March 1984)   |
|  | Uckun, F. et al., "TXU (Anti-CD7)-Pokeweed Antiviral Protein as a Potent Inhibitor of Human Immunodeficiency Virus", <i>Antimicrobial Agents &amp; Chemotherapy</i> , 42(2):383-388 (February 1998)  |
|  | Venkatachalam, T. K. et al., "Enhancing Effects of a Mono-Bromo Substitution at the Para Position of the Phenyl Moiety on the Metabolism and Anti-HIV Activity of D4T-Phenyl Methoxyalaninyl Phosphate Derivatives", <i>Bioorganic &amp; Medicinal Chemistry Letters</i> , Vol. 8, pp. 3121-3126 (1998). |
|  | Vig, R. et al., "Aryl phosphate derivatives of 3'-deoxythymidine are not potent anti-human immunodeficiency virus agents," <i>Antiviral Chemistry &amp; Chemotherapy</i> , Vol. 9, pp. 439-443 (©1998 International Medical Press).  |
|  | Vig, R. et al., "D4T-5'[p-Bromophenyl Methoxyalaninyl Phosphate] as a Potent and Non-Toxic Anti-Human Immunodeficiency Virus Agent", <i>Antiviral Chem. Chemother.</i> , Vol. 9(5), pgs. 445-448 (1998)  |
|  | Wang, L. et al., "In Vivo Biodistribution, Pharmacokinetic Parameters, and Brain Uptake of 5-Halo-6-methoxy (or ethoxy)-5, 6-dihydro-3'-azido-3'-deoxythymidine Diastereomers as Potential Prodrugs of 3'-Azido-3'-deoxythymidine", <i>J. Med. Chem.</i> , 39(4):826-833 (February 16, 1996)             |
|  | Wiebe, L. et al., "5-Halo-6-alkoxy-5, 6-dihydro-pyrimidine Nucleosides: Antiviral Nucleosides or Nucleoside Prodrugs", <i>Nucleosides &amp; Nucleotides</i> , 14(3-5):501-505 (May/June/July 1995)   |
|  | Wilborn, W. et al., "Scanning Electron Microscopy of Human Spermatozoa after Incubation with the Spermicide Nonoxynol-9", <i>Fertility and Sterility</i> , 39(5):717-719 (May 1983)  |
|  | Zarling, J. et al., "Inhibition of HIV Replication by Pokeweed Antiviral Protein Targeted to CD4 <sup>+</sup> Cells by Monoclonal Antibodies", <i>Nature</i> , 347(6288):92-95 (September 6, 1990)   |
|  |  |
|  |  |
|  |  |
|  |  |
|  |  |
|  |  |

|   |                 |
|---|-----------------|
| EXAMINER  | DATE CONSIDERED |
| EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form for next communication to the Applicant. |                 |